DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Division of Biostatistics and Epidemiology (HFM-215)

Memorandum

BLA NUMBER: *97-1251*

SPONSOR: *Novartis*

DATE: May 6, 1998

FROM: *Teresa Neeman, Ph.D.*

THROUGH: *Peter A. Lachenbruch, Ph.D., Chief, Biostatistics Branch*

SUBJECT: *Statistical Review : Simulect™ in the Prophylaxis of Acute Rejection in Renal Transplant*

TO: *Dr. David Essayan, Clinical Reviewer* Fred Miller
Division of Clinical Trial Design and Analysis (DCTDA) HFM-579

CC: *original/DCC/HFM-99*
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CHIB-201

BACKGROUND

Two Phase 3 studies were submitted in support of this application. The first, CHIB 201, was a multicenter, randomized, double-blind, placebo-controlled trial of Simulect™ in 381 subjects scheduled to receive cadaveric kidney transplant. A total of 21 centers in Belgium, Canada, France, Germany, Norway, Switzerland and the United Kingdom participated. Patients were enrolled between February 1995 and February 1996. The primary objective of the study was to assess the ability of Simulect™ to prevent acute rejection episodes within the first 6 months following transplant.

Comment: In the protocol dated 16 August 1995, it is stated in the statistical section (p. 52) that

the primary endpoint will be the percentage of patients experiencing at least one acute rejection episode during the first 3 months post-transplant. The secondary endpoints were the percentage of patients experiencing at least one acute rejection episode within 12 months, graft survival at 12 months, and overall patient survival at 12 months. However, in sections III and IV of the same protocol, the primary objectives were recently edited to read the incidence of acute rejection episodes at 6 months, with the secondary objectives focusing on 12 month follow-up. Although this change was made in the middle of the recruitment of patients, it reflects a clinically relevant benefit, and considered by the advisory committee to be the appropriate endpoint for solid organ transplant studies [redacted]. Moreover, the change does not have any real effect on the measurement of treatment effect, since the vast majority of the rejection episodes occurred in the first 2 months of the study. It is therefore unlikely that the endpoint was changed because of data being generated from the study.

PATIENT DISPOSITION

Although 381 subjects were randomized, one patient randomized to placebo (patient # [redacted] received neither study drug nor transplant. That patient was not considered in any of the analyses. In addition, 3 subjects in the Simulect™ arm and 2 subjects in the placebo arm received one dose of study drug, but were never transplanted. Four of these five patients were not included in the Intent-to-Treat analysis. The fifth patient, Patient [redacted] who was randomized to the placebo arm was inadvertently included in all of the analyses. The sponsor noted, however that this patient was considered in the analysis to be a treatment success, and therefore his inclusion only counted against the experimental drug. All transplanted patients received at least one dose of study drug.

	Simulect	Placebo
total randomized	193	188
did not receive study drug or transplant	0	1
received at least 1 dose of study drug	193	187
did not receive transplant	3*	2**
"ITT" population	190	185

* patient #s: [redacted]

** patient #: [redacted] was inadvertently included in the sponsor's ITT analysis, so their patient totals were 190 and 186, for the treatment group and the placebo group respectively.

Comments: The protocol states that all patients receiving at least one dose of study drug will be included in the ITT analyses for acute graft rejections and survival. If a patient does not receive the scheduled transplant because of a serious adverse event, he/she will be considered a failure for the primary endpoint. If the patient does not receive the scheduled transplant for any other reason, he/she will be "censored" in the primary endpoint analysis. This effectively means that they will not be included in the analysis. We should verify that the 5 patients who did not receive a transplant did not experience an adverse event.

Demographic and Baseline Data

The age, gender and race of the subjects appear to be well-balanced between the two randomized groups. The sponsor summarized these data in Table 9.2-1 (volume 83). This summary was verified by the statistical reviewer using the JMP data sets provided by the sponsor, and appears in the table below.

Demographic Variable		Simulect™	Placebo
Age (years)	N	193	188
	median	49	48
	(Q1,Q3)	(39,56)	(37, 57)
	min-max	18-74	18-73
Gender			
	male (%)	127 (66%)	119 (63%)
	female (%)	66 (34%)	69 (37%)
race			
	Caucasian (%)	182 (94%)	181 (96%)
	Black (%)	3 (2%)	1 (0.5%)
	Asian (%)	6 (3%)	5 (2.5%)
	Other (%)	2 (1%)	1 (0.5%)

ANALYSIS OF PRIMARY ENDPOINT/SPONSOR'S ANALYSIS

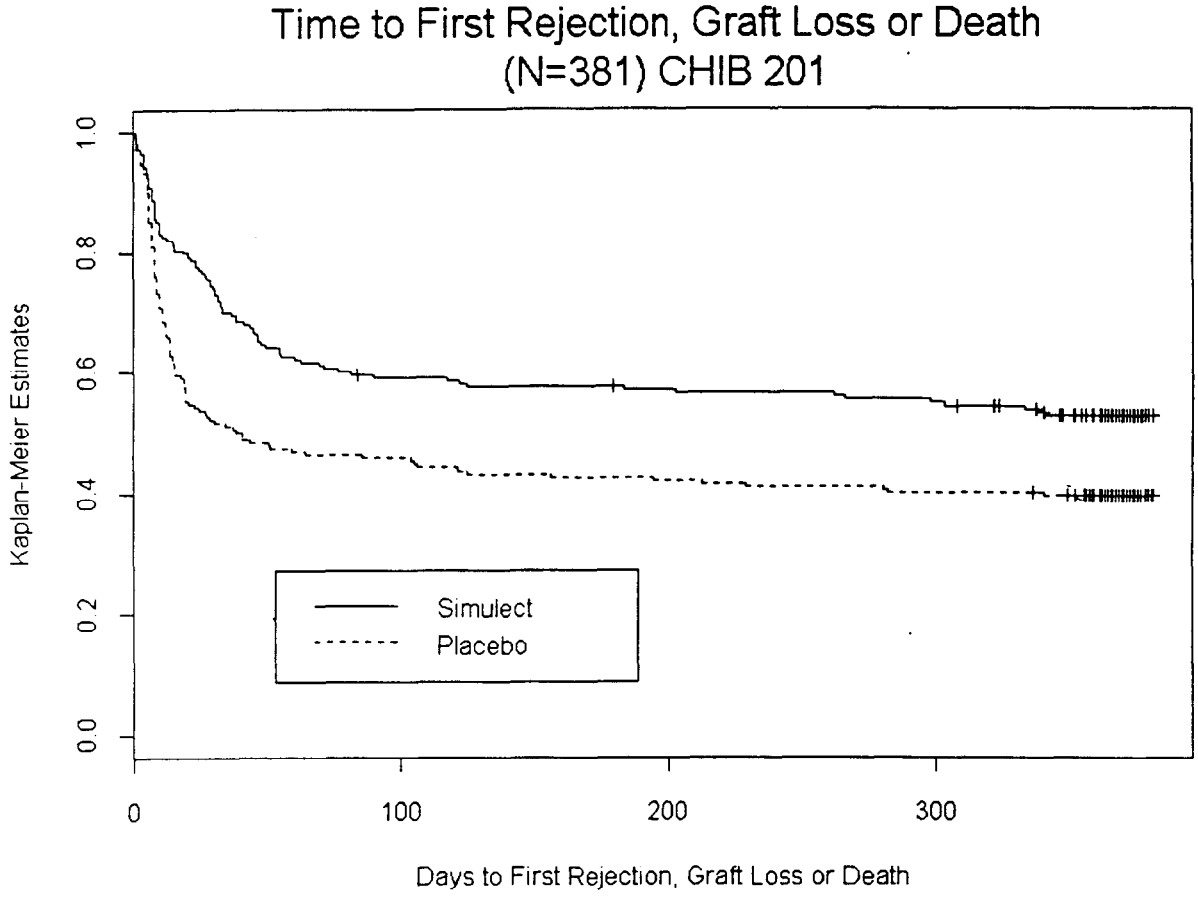
The sponsor's primary efficacy assessment compared the Kaplan-Meier estimates of patients in the two arms who had not yet experienced an acute rejection episode, a graft loss or death at 6 months post-transplant. Standard errors for these estimates were computed, and a p-value was generated for the difference of the Kaplan-Meier estimates using the statistic:

$$t = \frac{estimate[1] - estimate[2]}{\sqrt{se[1]^2 + se[2]^2}}$$

which is aymptotically normally distributed with mean 0 and variance 1, under the null

hypothesis. In addition, assuming asymptotic normality of the Kaplan-Meier estimates, the sponsor computed a 95% confidence interval around the difference of the two estimates. Numbers and percentages of patients in the two arms experiencing an acute rejection episode, a graft loss or death at 12 months post-transplant are summarized in the table below:

	Simulect™ (n=193)	Placebo (n=188)	total (N=381)
acute rejection, graft loss or death at 12 months	91 (47%)	114 (61%)	205 (54%)
no rejection, and followed over 12 months	92 (48%)	70 (37%)	162 (43%)
incomplete follow-up	7 (3.5%)	1 (.5%)	8 (2%)
no transplant	3 (1.5%)	3 (1.5%)	6 (1.5%)



This reviewer confirmed all of these analyses using —— software. The population evaluated was the 375 patients who received a transplant and at least one dose of study drug plus patient — from the placebo arm who was inadvertently included, who was followed for 358 days and classified as a treatment success. The results of this analysis appear in the table below.

Proportion of patients not experiencing acute rejection, graft loss or death:	Simulect™	Placebo	t-statistic (p-value)
at 6 months			
Kaplan-Meier estimate	0.579	0.425	3.02
standard error	0.036	0.036	(0.002)
at 12 months			
Kaplan-Meier estimate	0.535	0.398	2.8
standard error	0.036	0.036	(0.007)
log rank statistic 10.9 (chi-squared, 1 d.f.) p-value= 0.001			

The protocol (dated August 16 1995) states that a Cox proportional hazards model would be used to estimate the treatment effect, and the hypothesis test would be the likelihood ratio test. In addition, Kaplan-Meier estimates for 3-month survival would be computed and compared between randomized groups. Since Sections III-IV of the protocol were amended to state that primary endpoint would be the 6 month time point, it is assumed that the intention was to also amend the statistical section. As it happened, there were very few events between 3 months and 6 months, and the treatment effect was highly statistically significant, so there was little difference in the choice of endpoint.

Primary Endpoint/ Exploratory Analyses

Covariate Analysis: A number of covariates were used to model time to death, graft loss or acute rejection using a Cox proportional hazards model. The ability of a covariate to predict time to event was measured using the likelihood ratio statistic, which is approximately chi-squared under the null hypothesis. Only treatment assignment was considered to be a significant predictor of time to event. Other covariates evaluated were patient age, gender, race, HLA mismatch, cold ischemia time, and presence or absence of diabetes. This analysis was done using —— software and the " ——- " function. A summary of the results appears in the table below:

covariate	Likelihood ratio statistic	degrees of freedom	p-value	n	group doing better
treatment group	10.2	1	0.001	381	Simulect™
Age	0	1	0.95	381	*
Sex	1.9	1	0.17	381	men
Race	0.31	3	0.96	381	*

covariate	Likelihood ratio statistic	degrees of freedom	p-value	n	group doing better
HLA mismatch	0.74	1	0.39	376	more matches
cold ischemia time	0.82	1	0.36	373	less time
diabetes	1.4	1	0.24	381	diabetes

There were only 22 patients diagnosed with diabetes. Although the numbers are small, there was a greater treatment effect observed in these patients than in the non-diabetic patients. The tabel below illustrates this difference. Treatment interactions were also evaluated for HLA mismatch and gender, and there were no apparent interactions. For this analysis, only transplanted patients were included.

Subgroup		Simulect # reject, etc. (%)	Placebo # reject, etc. (%)	odds ratio
gender	male	57/126 (45%)	69/118 (58%)	1.70
	female	31/64 (48%)	43/68 (63%)	1.83
#HLA mismatches	≤ 1	8/13 (62%)	9/17 (53%)	0.70
	2	16/41 (39%)	20/40 (50%)	1.56
	3	25/63 (40%)	51/74 (69%)	3.37
	4	23/43 (53%)	20/36 (56%)	1.09
	> 4	16/29 (55%)	11/18 (61%)	1.28
diabetes	no	85/177 (48%)	106/177 (60%)	1.62
	yes	3/13 (23%)	6/9 (67%)	6.67

Treatment by Center Effects: The efficacy suggested by the overall test statistic was explored in each of the 21 study sites. As can be seen from the table below (all centers with at least 14 enrolled patients), there was consistency of treatment effect across the centers.

Study Site	death, graft loss or rejection	Simulect™	Placebo	total
23 (N=41)	event no event	10 (48%) 11 (52%)	14 (70%) 6 (30%)	24 (58%) 17 (42%)
22 (N=40)	event no event	13 (65%) 7 (35%)	13 (65%) 7 (35%)	26 (65%) 14 (35%)
31 (N=33)	event no event	3 (18%) 14 (82%)	6 (38%) 10 (62%)	9 (27%) 24 (73%)
24 (N=27)	event no event	8 (62%) 5 (38%)	11 (79%) 3 (21%)	19 (70%) 8 (30%)
33 (N=21)	event no event	6 (60%) 4 (40%)	10 (90%) 1 (10%)	16 (76%) 5 (24%)
62 (N=20)	event no event	6 (60%) 4 (40%)	9 (90%) 1 (10%)	15 (75%) 5 (25%)
71 (N=20)	event no event	3 (30%) 7 (70%)	6 (60%) 4 (40%)	9 (45%) 11 (55%)
32 (N=19)	event no event	8 (80%) 2 (20%)	5 (56%) 4 (44%)	13 (68%) 6 (32%)
26 (N=16)	event no event	2 (25%) 6 (75%)	5 (62%) 3 (38%)	7 (44%) 9 (56%)
28 (N=15)	event no event	2 (29%) 5 (71%)	2 (25%) 6 (75%)	4 (27%) 11 (73%)
81 (N=15)	event no event	2 (25%) 6 (75%)	2 (29%) 5 (71%)	4 (27%) 11 (73%)
11 (N=14)	event no event	2 (25%) 6 (75%)	2 (33%) 4 (67%)	4 (29%) 10 (71%)
13 (N=14)	event no event	4 (57%) 3 (43%)	2 (29%) 5 (71%)	6 (43%) 8 (57%)
25 (N=14)	event no event	2 (29%) 5 (71%)	4 (57%) 3 (43%)	6 (43%) 8 (57%)
41 (N=14)	event no event	3 (50%) 3 (50%)	4 (50%) 4 (50%)	7 (50%) 7 (50%)

Only centers 32 (19 patients), 28 (15 patients), and 13 (14 patients) had a higher percentage of events in the Simulect™ arm. The total event rate among the centers varied between 25-75%. Since the randomization was stratified by center, a likelihood ratio test of treatment effect using Cox proportional hazards was performed using study sites as strata. A p-value of less than 0.001 was further evidence that the treatment effect is statistically significant.

Sensitivity Analysis: Six subjects were not included in the sponsor's intent-to-treat analysis, three who had been randomized to placebo, and three who had been randomized to Simulect™. None of these patients received a kidney transplant, although five of the six received one dose of study drug. The sixth patient, who received neither study drug nor transplant, was in the placebo group. In order to maximally bias the test statistic against the experimental arm, the three subjects not receiving a transplant in the placebo arm were censored on their last day of contact, whereas the subjects randomized to the placebo arm were considered to have an event on day 1. Subject —— from whom no follow-up was available, was arbitrarily censored on day 365. The groups (193 in Simulect™ arm and 188 in placebo arm) were compared using a log rank test. A p-value of 0.003 supports the hypothesis of a treatment effect, in spite of the bias against the treatment arm.

Categorical Analysis: One can also consider breaking out the categories of rejection, graft loss, and death, to investigate the possibility that the "events" observed in the Simulect arm were of a different or more serious type than those observed in the placebo arm. Although several subjects experienced more than one event, each subject was classified according the worst event experienced. For example, if a subject had a acute rejection episode followed by a graft loss, then he/she was classified as having experienced a graft loss. Since this was an exploratory analysis, only the 375 patients who had received a transplant were included in this analysis. A summary of the data appears in the table below:

	no event	acute rejection	graft loss	death	no transplant	total
Simulect	102 (53%)	59 (31%)	20 (10%)	9 (5%)	3 (2%)	193
Placebo	73 (39%)	83 (44%)	24 (13%)	5 (3%)	3 (2%)	188

A Komolgorov-Smirnov test was used to test the equality of the two distributions. The software —— was used to compute an exact 2-sided p-value, which was 0.007. In addition, this software tests the hypotheses that one distribution is stochastically larger than the other. In this case, a distribution is stochastically larger if there tend to be fewer bad events and more good events. The K-S test that Simulect is "better" yielded an exact p-value of 0.004. The K-S test that Simulect is "worse" yielded an exact p-value of 0.54. The results of this analysis confirm earlier analyses of an overall treatment effect.

Severity of Rejection: Some patients experienced multiple rejections. For the purposes of this analysis, patients were classified by the most severe grade. These data were extracted from the SAS data set ———— The distribution of the severity of the rejection for each of the

randomized groups is displayed in the table below. There is no evidence that the treatment arm experienced more severe rejection episodes than the control arm.

	no rejection episode	borderline changes	mild acute rejection	moderate acute rejection	severe acute rejection	no transplant	missing
Simulect (n=193)	118 (61%)	4 (2%)	22 (11%)	32 (17%)	5 (3%)	3 (2%)	9 (5%)
Placebo (n=188)	84 (45%)	12 (6%)	33 (18%)	36 (19%)	11 (6%)	2 (1%)	10 (5%)

Number of Rejection Episodes per Patient: The number of rejection episodes per patient was tabulated. There is no evidence that the number of episodes among patients who experience rejection is greater in the treatment arm compared with the control arm.

	no rejection episode	Number of Rejection Episodes				no transplant
		1	2	3	4	
Simulect (n=193)	118 (61%)	49 (25%)	17 (9%)	5 (3%)	1 (<1%)	3 (2%)
Placebo (n=188)	84 (45%)	77 (41%)	19 (10%)	5 (3%)	1 (<1%)	2 (1%)

CHIB-352

BACKGROUND

The second trial had the same study design as the first trial. It was also a multicenter, randomized, double-blind, placebo-controlled trial of Simulect enrolling 348 subjects receiving renal allografts in a total of 25 centers in the United States. While patients in the previous study ——— received only cadaveric kidney transplants, some patients in this study also received kidneys from living donors. Patients were enrolled between June 1995 and May 1996, with the last patient completing 12 month follow-up in May 1997. As with the previous study, the primary objective was to assess the ability of Simulect to prevent acute rejection episodes within the first 6 months following transplant.

PATIENT DISPOSITION

Of the 348 randomized patients, one subject (—) in the Simulect arm and one subject (—) in the placebo arm received one dose of study drug, but were never transplanted. The protocol specified that all patients would be included in the primary analysis (ITT); however, subsequently it was decided that only patients receiving transplants would be included in the Intent-to-Treat population. Although we performed a sensitivity analysis to verify the robustness of the conclusions based upon 346 subjects, the strength of the evidence of a treatment effect is such that these additional analyses are unnecessary.

	Simulect	Placebo
total randomized	174	174
did not receive study drug or transplant	0	0
received at least 1 dose of study drug	174	174
did not receive transplant	1*	1**
"ITT" population	173	173

* patient # —
** patient # —

D .nographic and Baseline Data

The age, gender and race of the subjects appear to be well-balanced between the two randomized

groups. The sponsor summarized these data in Table 9.2-1 (volume 85). This summary was verified by the statistical reviewer using the JMP data sets provided by the sponsor, and appears in the table below.

Demographic Variable		Simulect	Placebo
Age (years)	N	193	188
	median	49	48
	(Q1,Q3)	(39,56)	(37, 57)
	min-max	18-74	18-73
Gender			
	male (%)	127 (66%)	119 (63%)
	female (%)	66 (34%)	69 (37%)
race			
	Caucasian (%)	182 (94%)	181 (96%)
	Black (%)	3 (2%)	1 (0.5%)
	Asian (%)	6 (3%)	5 (2.5%)
	Other (%)	2 (1%)	1 (0.5%)

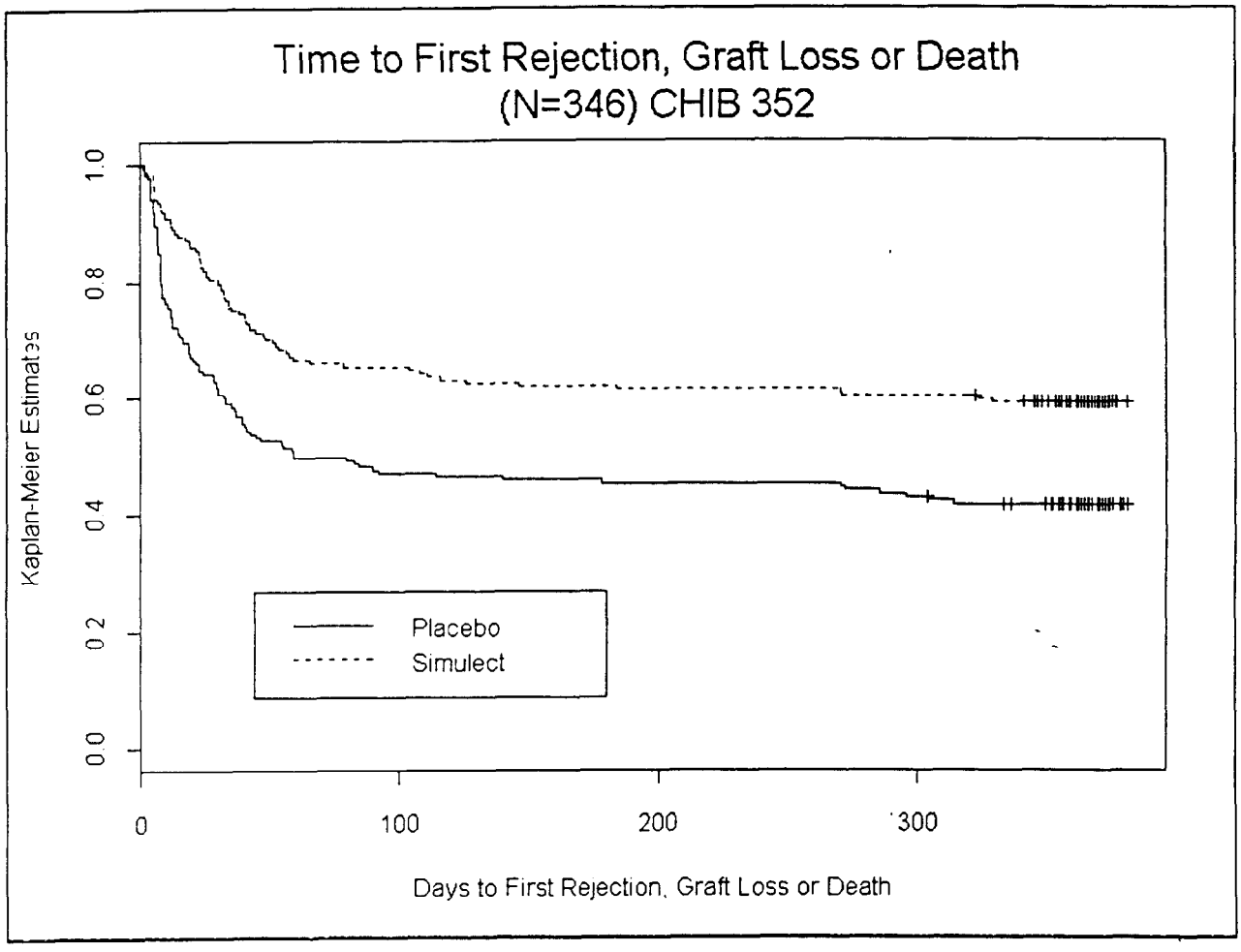
PRIMARY ENDPOINT ANALYSIS

The primary endpoint in this study was the incidence of acute rejection, graft loss or death within 6 months of the transplant. Since patients were to be followed for 12 months, data on the incidence of acute rejection, graft loss or death within 12 months of transplant was also collected. This reviewer confirmed the summary tables in the study report for both the 6 month and the 12 month data from the SAS data sets provided by the sponsor. The table below summarizes the number of patients experiencing first rejection, graft loss or death following renal transplant.

Death, graft loss or rejection	Simulect (N=173)	Placebo (N=173)	total (N=346)
within 6 months	66 (38%)	95 (55%)	161 (47%)
within 12 months	71 (41%)	101 (58%)	172 (50%)

According to the protocol, patients who discontinued before the 12 month follow-up period and prior to reaching an endpoint were censored on the day of last contact. A Kaplan-Meier estimate of the proportion alive and rejection-free was computed for each of the randomized groups and compared, as in Protocol 201, using a two-sample t-test. In this study there were no censored patients before day 300, so the Kaplan-Meier estimates for the 6 month endpoint are the same as the proportion of patients alive and rejection-free at 6 months. Also, the estimate of the standard error is the same as the estimate of standard error for a binomial proportion. The difference between the two-sample t-test proposed in the protocol and a test of two proportions lies in the

denominator of the test statistic. In the two sample t-test, the variances are not pooled, while in the test of proportions, the denominator is the estimate of the standard error under the null hypothesis of no difference in the two proportions. As it happens, the two-sample t-test proposed in the protocol is roughly equivalent to a test of proportions (assuming asymptotic normality), or a chi-squared test. For the 12 month endpoint, there were two patients (— in the placebo arm and — in the Simulect arm) censored on days 304 and 322, respectively so the Kaplan-Meier estimates are slightly lower than the proportion observed alive and rejection-free. A comparison of the Kaplan-Meier estimates at 12 months between the randomized groups using the two-sample t-test will give essentially the same p-value as a comparison using a test of two proportions (or a chi-squared test).



Proportion of patients not experiencing acute rejection, graft loss or death:	Simulect (N=173)	Placebo (N=173)	test statistics
at 6 months			t-test
Kaplan-Meier estimate	0.62	0.45	t=3.2
standard error	0.037	0.038	p-value- 0.002
proportion alive, no rejection	0.62	0.45	Z-test
standard error	0.037	0.038	Z=3.1
			p-value- 0.002
at 12 months			t-test
Kaplan-Meier estimate	0.59	0.42	t=3.2
standard error	0.037	0.038	p-value-0.002
proportion alive, no rejection	0.59	0.42	Z-test
standard error	0.037	0.038	Z=3.2
			p-value- 0.002

This reviewer also repeated the sponsor's analysis that in an overall comparison of time-to-event using a log-rank test, the p-value of 0.0002 was consistent with the conclusion of treatment effect as seen in other analyses.

Sensitivity Analysis: The Kaplan-Meier estimates are unbiased estimates of expected proportions when the censoring mechanism is independent of the failure time. Since this may not be an appropriate assumption in this trial, one should also consider how the groups might have compared under the most conservative assumptions: all censored patients in the treatment arm are classified as failures on the day of last contact, while censored patients in the control arm are classified as successes at the 12 month follow-up. It is evident that, given the small numbers of censored patients and the large treatment effect, that this more conservative analysis will not alter the conclusion of a clear treatment effect. (Z=3.1, p-value- 0.002)

Cox Proportional Hazards Model: Because all of the patients on this study had complete six month follow-up, one can assess covariates in either a logistic regression model or a proportional hazards model. For two-level factors such as sex, treatment group, donor type, the coefficient estimates in a logistic regression model correspond to the log odds ratio computed from a corresponding 2x2 table. For continuous variables such as age, the coefficient estimate corresponds to the log odds ratio per unit change. In contrast, the coefficients estimated in a Cox proportional hazards model for a two-level factor correspond to the log of the hazard ratio of the two levels. For continuous variables, the coefficient estimate is the log of the hazard ratio of a unit change in the continuous variable. The hazard ratio is a first order approximation of the odds ratio, and while they may not be the same, the estimates will always go in the same direction, in the sense that when the hazard ratio is greater than one, the odds ratio will also be greater than

one, and conversely. Following the protocol, we tested the significance of several covariates separately using the Cox proportional hazards model. We repeated the exercise for the logistic regression model, and found no substantive differences in any of the significance levels. The results of the logistic regression models appear in one of the appendices. The results for the marginal Cox models appear in the table below.

Covariate	hazard ratio	likelihood ratio	p-value (likelihood ratio)	group doing better
treatment group	0.57	12.4	< 0.001	Simulect
age	1.0	0	1.0	*
sex	0.8	1.8	0.19	women
Afro-American vs. other	1.32	2.77	0.10	other
living donor vs. cadaveric donor	0.737	2.98	0.08	living donor
HLA mismatch	1.28	18.2	< 0.001	fewer
diabetes vs. no diabetes	0.911	0.25	0.61	diabetics
treatment group * HLA mismatch	0.65 1.3	32.6	< 0.001	*

The only statistically significant covariates appear to be treatment group assignment and HLA mismatch. When the two covariates were combined into a single model, the hazard ratio estimates are essentially unchanged, and both covariates are significant predictors of outcome. As one can see from the table below, the treatment effect remains fairly consistent across the numbers of HLA mismatches.

Number of HLA mismatches	# (%) patients with primary outcome (6 months)		
	Simulect	Placebo	Total
0	0/1 (0%)	0/1 (0%)	0/2 (0%)
1	1/5 (20%)	3/7 (43%)	4/12 (33%)
2	7/22 (32%)	6/16 (38%)	13/38 (34%)
3	12/41 (29%)	18/44 (41%)	30/85 (35%)
4	13/35 (37%)	21/39 (54%)	34/74 (46%)
5	16/37 (43%)	30/43 (70%)	46/80 (57%)
6	17/32 (53%)	17/23 (74%)	34/55 (62%)

Heterogeneity of Treatment Effect: Treatment effect in various subgroups was assessed and compared to look for differences in treatment effect. The endpoint for this analysis was acute

rejection, graft loss or death at 12 months. No treatment by subgroup interactions were found to be statistically significant at the 0.10 level. A summary of these findings appears in the table below:

subgroup		Simulect # reject, etc. (%)	Placebo # reject, etc. (%)	odds ratio
gender	male	45/111 (41%)	66/108 (61%)	0.43
	female	27/63 (43%)	36/66 (55%)	0.62
donor type	living	17/54 (31%)	25/51 (50%)	0.48
	cadaveric	54/119 (45%)	76/122 (62%)	0.50
race	Afro-Amer.	22/46 (48%)	38/59 (64%)	0.49
	all other	50/127 (39%)	64/115 (56%)	0.52
diabetes	no	54/124 (44%)	80/135 (59%)	0.53
	yes	18/50 (36%)	22/39 (56%)	0.43

Categorical Analysis: Patients were classified according to their worst outcome: acute rejection, graft loss or death. In the treatment arm, there were 65 patients who experienced acute rejection. Seven of these patients went on to experience graft failure or death. In the placebo arm, 95 patients experienced an acute rejection episode. Eleven of these patients also experienced a graft loss or death. A summary of these data is presented in the table below:

	no event	acute rejection	graft loss	death	no transplant	total
Simulect	102 (59%)	58 (33%)	8 (5%)	5 (3%)	1 (0.5%)	174
Placebo	72 (41%)	84 (48%)	10 (6%)	7 (4%)	1 (0.5%)	174

Severity of Rejection: Some patients experienced multiple rejections. For the purposes of this analysis, patients were classified by the most severe grade. These data were extracted from the SAS data set _____ The distribution of the severity of the rejection for each of the randomized groups is displayed in the table below. There is no evidence that the treatment arm experienced more severe rejection episodes than the control arm.

	no rejection episode	borderline changes	mild acute rejection	moderate acute rejection	severe acute rejection	no transplant	total
Simulect	108 (63%)	1 (0.5%)	26 (15%)	31 (18%)	4 (2%)	1 (0.5%)	174
Placebo	78 (47%)	4 (2%)	38 (23%)	37 (22%)	10 (6%)	1 (0.5%)	174

Number of Rejection Episodes per Patient: The number of rejection episodes per patient was tabulated. There is no evidence that the number of episodes among patients who experience rejection is greater in the treatment arm compared with the control arm.

	no rejection episode	Number of Rejection Episodes					total
		1	2	3	4	6	
Simulect	108 (63%)	46 (26%)	11(6%)	3 (2%)	4 (2%)	1 (0.5%)	173
Placebo	78 (47%)	58 (33%)	29 (17%)	7 (4%)	1 (.5%)	0 (0%)	173

CONCLUSIONS

There was evidence of a treatment effect in the two trials CHIB 201 and CHIB 352 with respect to the prospectively defined primary endpoint. This effect was consistent across a variety subgroups and across centers. There was no evidence that the severity of the rejections or the number of rejections greater than one was different between the two randomized groups. The number of HLA mismatches was an important prognostic variable, and the treatment effect appeared to be consistent across all levels of HLA mismatch. Both studies support the licensure of this product.

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